

HIV WANTS TO BE YOUR FRIEND

RESEARCHERS MAY MAKE MEDICINE
OUT OF THE AIDS VIRUS



AIDS researcher Flossie Wong-Staal: "We started thinking, Hah! Maybe the best vector [for genetic therapy] is HIV itself."

By Mark Schoofs

Traditionally, medicine has focused on attacking disease—antibiotics kill bacteria, surgery removes tumors, AZT blocks HIV. But now, researchers are trying to make the body better at defending itself. With a technique called "gene therapy," they are devising ways to rewire a patient's DNA so that the body itself can overcome diseases.

There are enormous technical tangles to be unraveled, but in theory gene therapy is simple and has almost infinite uses. Many cancers are caused by a genetic mutation; reverse that mutation and the cancer will be halted in its tracks. Diabetes is caused by the body's inability to make insulin; inscribe a genetic recipe for insulin into the body's DNA, and diabetics could throw away their syringes.

But gene therapy involves a tremendous irony. It works by retooling a virus. First it is stripped of the elements that cause disease, then it is loaded with therapeutic genetic "cargo." Astonishingly, one of the best viruses for delivering such cargo could be the killer HIV. And one of the diseases that HIV gene therapy might be best at fighting is AIDS.

Turning HIV against itself, says leading researcher Didier Trono, "would be sweet revenge."

THERE ARE MANY WAYS gene therapy could help fight AIDS. Researcher Flossie Wong-Staal is working on one approach.

HIV contains two strands of RNA. But certain enzymes, called ribozymes, cut RNA. Remarkably versatile, ribozymes can easily be engineered to cut only certain kinds of RNA at very specific locations. Put a few of the right ribozymes in a cell with HIV and, voilà, you have harmless genetic confetti.

In the lab, this strategy disabled HIV.

protease-inhibitor wonder drugs. So Wong-Staal conducted rudimentary gene-therapy trials. She took a mouse leukemia virus, rendered it unable to replicate, and loaded it with genes for the anti-HIV ribozymes. In a test tube, she infected cells from HIV-positive patients with the therapeutic mouse virus. It did what it was supposed to: Some of the cells were able to produce the ribozymes on their own, "proving the principle" that gene therapy could effectively deliver anti-HIV cargo.

Wong-Staal decided to work with the mouse virus because it doesn't cause disease in humans and because, like HIV, it writes its genetic code onto the host cell's chromosomes, making a permanent change in the DNA. The therapeutically infected cell—and all its progeny—will carry the ability to produce the ribozymes forever.

But in the real world, the mouse virus is a bad delivery vehicle. One of its main drawbacks is that it can't infect nondividing cells (including many in the nervous system, liver, and other organs). HIV, on the other hand, *does* infect nondividing cells—particularly the immune system's T-cells and macrophages. They rarely divide, so the mouse virus wouldn't be able to strengthen the cells HIV attacks.

But ideally, HIV could be tailored to infect bone-marrow "stem cells," which produce T-cells. If therapeutic cargo could be delivered to the stem cells, then all the cells they produce would be able to cut HIV to ribbons. Indeed, it might suffice to therapeutically alter just 5 per cent of the stem cells. While HIV would kill the other 95 per cent, the small pool of modified cells would repopulate the body with HIV-destroying progeny.

The mouse virus has another shortcoming: It infects virtually any dividing cell, so it would waste much of its cargo by delivering it to cells that don't need it. This is a big problem, because in gene therapy, the patient would likely get only one shot—literally. After the first injection, the body's immune system would

rendering any follow-up injections useless.

The ideal "vector"—a virus that delivers the therapeutic cargo—would be one that infects both dividing and nondividing cells, but only the ones that HIV targets. So, Wong-Staal says, "we started thinking, Hah! Maybe the best vector is HIV itself."

IN LABS ALL OVER the world, gene-therapy researchers are trying to harness HIV, and they are hoping to treat many diseases besides AIDS. That's because, as Trono points out, many of the cells that doctors want to target rarely or never divide. A few other viruses, such as the one that causes the common cold, can also infect nondividing cells. But very few viruses can do that and permanently install their genetic cargo into the patient's DNA. That's what makes HIV so appealing. It can do both.

Trono points to Parkinson's disease, which is caused by the brain's inability to synthesize a neurotransmitter called dopamine. If cells in the brain could be genetically rewired to carry out that task, then presto, Parkinson's would be cured. HIV would be a prime candidate for treating Parkinson's, Trono notes, because "neurons never divide after we reach a young age" and the ability to synthesize dopamine would, of course, need to be permanent.

One of the easiest diseases to cure might be hemophilia, which is brought on by the lack of a factor that causes blood to clot. But this clotting factor could be produced anywhere in the body, as long as it was able to seep into the blood, says Trono. (This adds another layer of irony, since hemophiliacs have been devastated by AIDS.)

But *easy* is a relative term. "These viruses have taken billions of years to get to where they are," says Trono's colleague Inder Verma. "We

think we can cut and paste to get what we want," he says, but every component "has a meaning." Indeed, one therapeutic virus has worked in mice but not monkeys. Or a virus that is engineered to infect cells in one organ might not penetrate those of another. Finally, while gene-therapy trials are currently taking place in humans, no cures have been demonstrated so far.

ESPECIALLY WITH HIV, the most troubling problem is safety. Even if the virus were stripped of one of its key components, it could reconstruct itself. Through a kind of viral sex called "recombination," HIV can mix with other retroviruses, pick up some of their genes, and possibly regain the parts scientists strip away. So how can HIV be made safe enough to inject into human beings? By gutting so much of its genetic core that what remains is only a husk of the original pathogenic virus.

That's exactly what Trono has done. He and Verma set the gene-therapy field buzzing last year when they made the first HIV vector that worked in a living animal (it delivered a gene to the brain cells of rats). They deleted two genes from HIV, leaving the virus unable to replicate or cause disease. At a recent symposium, Trono described a similar experiment—but with a much safer version of the virus. Out of HIV's nine genes, Trono removed five. It is highly unlikely that HIV could reacquire so much of itself.

Still, many scientists suggest using viruses that have the same advantages as HIV without causing disease in humans. They point to equine infectious anemia virus, or to simian and bovine cousins of HIV. But using animal viruses is no panacea. Through recombination, they could acquire the ability to cause disease in people. And even a benign virus could trigger cancer. That's a risk with any virus that changes a patient's DNA.

For many patients, HIV-based gene therapy would be scary, and would doubtless require years of safety tests. "But I think that's a moot point for an AIDS patient," says Wong-Staal. "He

of HIV."